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Infection with human herpes virus type 8 in an area at high prevalence for hepatitis C virus infection in southern Italy

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SUMMARY. The Campania Region is a geographical area of southern Italy characterized by high incidence rates of hepatocellular carcinoma and of classic Kaposi's sarcoma. Epidemiological investigations carried out among different population groups in this region have found high prevalence rates of both hepatitis C virus (HCV) and human herpesvirus type 8 (HHV-8). To assess co-infection rates of HCV and HHV-8, we carried out a cross-sectional seroepidemiological study prevalence in Pomigliano d'Arco, a Health District of Campania located 20 km away from Naples. The overall rate of HCV/HHV-8 co-infection was 3.1%, 3.5% among men and 2.7% among women. No difference emerged in the HCV/HHV-8 co-infection rates according to seropositivity for HCV infection, either overall (Mantel Haenszel odds ratio = 1.2, 95% CI: 0.6–2.6) or when the analysis was stratified by gender. These findings support the hypothesis that in Campania common routes of transmission are rarely shared by HCV and HHV-8 infections. Local factors may result in different epidemiological patterns for these two viral infections. However, our findings have important public health implications, especially in Mediterranean countries where HCV and HHV-8 infections are endemic.

Keywords: co-infection, hepatitis C virus, human herpesvirus type 8, prevalence, southern Italy.

INTRODUCTION

The Campania Region is a geographical area of southern Italy characterized by high incidence rates of hepatocellular carcinoma and of classic Kaposi's sarcoma (KS) [1,2]. Epidemiological investigations carried out among different population groups in this region have found high prevalence rates of both hepatitis C virus (HCV) and human herpesvirus type-8 (HHV-8) infections. Fifteen per cent of males over the age of 40 years was infected with HCV, and 20% of males over the age of 50 years were seropositive for HHV-8 antibodies [3–6].

In the past decades, several factors related to disadvantaged social conditions might have favoured the spread of HCV infection in the Campania Region, including iatrogenic transmission through the extensive use of glass syringes [3,4]. There are no well-defined explanations for the elevated spread of HHV-8 [6,7]. In addition, concomitant infection with HCV and HHV-8 has never been investigated in Italy.

To assess co-infection rates of HCV and HHV-8, we carried out a cross-sectional seroepidemiological prevalence study in Pomigliano d'Arco, a Health District of Campania located 20 km away from Naples.

METHODS

We used serum samples collected during 2000 and 2001 for a case–control study of risk factors for classical KS. The methods and initial findings have been published [8]. It is worth stressing here that the individuals included in the present investigation were selected according to age (≥35 years), no evidence of KS or other malignant disorder, and no history of male homosexual intercourse, intravenous drug use or infection with human immunodeficiency virus.

The serological diagnosis of HCV infection was performed using a third generation ELISA test (Ortho Diagnostic Systems, Raritan, NJ, USA). Samples yielding positive results were re-tested by recombinant immunoblot (HCV RIBA3.0, Ortho), and none were negative.

Abbreviations: HCV, hepatitis C virus; HHV-8, human herpes virus type 8.

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Table 1 Distribution of 351 individuals according to age and seropositivity for HCV and HHV-8

	HCV serology		HHV-8 serology		
Age range	Positive (prevalence) *n* (%)	Negative (*n*)	Positive (prevalence) *n* (%)	Negative (*n*)	Total
≤55	3 (5.5)	52	8 (14.5)	47	55
56–65	15 (15.5)	82	10 (10.3)	87	97
66–75	22 (18.5)	97	20 (16.8)	99	119
≥76	22 (27.5)	58	14 (17.5)	66	80
Total	62 (17.7)	289	52 (14.8)	299	351

Antibodies against HHV-8 latent nuclear antigens were detected after a 1:120 dilution of patient sera by immunofluorescence assay, using the BCBL-1 cell line with and without induction by tetradecanoyl phorbol-ester acetate (TPA). All positive sera were also re-tested at the same dilution with the Molt 4 cell line to exclude nonspecific cellular reactivity. Sera that had antibody reactivity both with and without TPA induction were considered seropositive.

Differences among categorical variables were analysed using the chi-square test or two-tailed Fisher's exact test. The association between HCV serostatus and seropositivity for HHV-8 antibodies was estimated by means of the odds ratio (OR) and 95% confidence interval (CI), separately by sex and adjusted for age (≤55, 56–65, 66–75 and ≥76 years) with the Mantel Haenszel (MH) procedure [9].

RESULTS

The current cross-sectional seroepidemiological investigation included 351 individuals (202 men and 149 women; median age, 67 years). Overall HCV seroprevalence was 17.7% (95% CI: 13.7–21.7), It significantly increased with age: 5.5, 15.5, 18.5 and 27.5% among those aged ≤55, 56–65, 66–75 and ≥76 years, respectively (chi-square trend = 6.702, $P = 0.01$) (Table 1). The prevalence of HCV infection was not significantly higher in men (18.3%) than in women (16.8%) ($P = 0.4$).

Overall, antibodies to HHV-8 were detected in 14.8% of the individuals investigated (95% CI: 11.1–18.5). Unlike HCV infection, HHV-8 infection did not increase significantly with age: 14.5, 10.3, 16.8 and 17.5% among those aged ≤55, 56–65, 66–75 and 76 years or older, respectively (chi-square trend = 0.709, $P = 0.4$) (Table 1). It did not differ significantly between men (14.4% positive) and women (15.4% positive) ($P = 0.4$).

Table 2 shows the seropositivity for HHV-8 antibodies according to HCV infection. The overall rate of HCV/HHV-8 co-infection was 3.1%, 3.5% among men and 2.7% among women. No difference emerged in the HCV/HHV-8 co-infection rates according to seropositivity for HCV infection, either overall (MH-OR = 1.2, 95% CI: 0.6–2.6) or when the analysis was stratified by gender. Of the 62 individuals who were seropositive for HCV infection, 11 (17.7%, 95% CI: 13.7–21.7) were also seropositive for HHV-8, whereas 41 of the 289 HCV-seronegative individuals were seropositive for HHV-8 (14.2%, 95% CI: 10.5–17.8).

Table 2 Seropositivity for HHV-8 antibodies according to HCV exposure, stratified by gender

	HCV serology (*n*)	HHV-8 seropositivity *n* (%)	MH-OR (95% CI)
Males			
Negative	165	22 (13.3)	1*
Positive	37	7 (18.9)	1.4 (0.5–3.6)
Females			
Negative	124	19 (15.3)	1*
Positive	25	4 (16.0)	1.1 (0.3–3.6)
All			
Negative	289	41 (14.2)	1*
Positive	62	11 (17.7)	1.2 (0.6–2.6)

*Reference category.
MH-OR = Mantel Haenszel odds ratios adjusted for age and gender (when appropriate).

DISCUSSION

Only seven men and four women among the 351 individuals herein investigated were positive to both HHV-8 and HCV infections. As confirmed by other studies, in southern Italy the HCV positive rate increases with age while that for HHV-8 is constant in the different age categories [4–6].

These findings support the hypothesis that in Campania common routes of transmission are rarely shared by HCV and HHV-8 infections. Local factors may result in different epidemiological patterns for these two viral infections. HCV is predominantly transmitted by blood inoculation. Excluding injection drug users, as we did in the current study, most of the high HCV seroprevalence in Campania can be attributed to iatrogenic transmission via re-used but insufficiently

sterilized glass [3] syringes and other nondisposable medical devices, as the risk of transfusion-transmitted infections is low in Italy [10]. In southern Italy, including Campania, HHV-8 is endemic. Probably, it has been in the population for centuries and reflects both sexual acquisition among adults and nonsexual acquisition among children and adults. This is also true in parts of Africa where KS was seen in children even before the advent of the acquired immunodeficiency syndrome [11,12].

In a nonendemic population of the USA, two studies have associated HHV-8 infection with HCV, injection drug use and sexually transmitted infections [13,14], but there are no results for the general population. If transmission of HHV-8 by blood inoculation occurs at all, our findings and those noted previously in Sicily and the USA, indicate that it is highly inefficient [6,8,13]. However, additional work is needed to evaluate possible transfusion transmission of HHV-8 in particular.

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